REMARKS

Claims 11, 13, and 17-25 are currently pending and under consideration. Claims 11, 13, 24 and 25 have been amended to recite that the extracellular domain of the soluble IL-21R is at least 90% identical to amino acids 20-235 of SEQ ID NO:4 (rather than 85% identical to amino acids 20-235 of SEQ ID NO:4). Support for this amendment may be found at page 18, line 16 to page 19, line 10. Consideration of the amendments and the remarks presented herein is respectfully requested.

I. Withdrawn Rejection based on 35 U.S.C. §112, 2nd Paragraph

The Examiner has withdrawn the rejection of claims 11, 13, 24 and 25 under 35 U.S.C. §112, 2nd paragraph, stating that the claims now recite the article "the" when referring to IL-21R. Applicants note that in the previous Office Action, the Examiner required clarification of the phrase "soluble fragment of an IL-21R" as recited in claims 11, 13, 24, and 25 (Office Action, dated March 7, 2006 at p. 8). Specifically, the Examiner contended that "[t]here is only one known IL-21 receptor (i.e. SEQ ID NO:4)," and thus the use of the term "an" before "IL-21R" rendered the claims unclear (*id.*). In the previous Amendment and Response, Applicants presented the following amendment to the noted claims:

> a soluble ~~fragment of an~~ IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4.

(Amendment and Response, dated June 7, 2006, at pp. 2-5). In that Response, Applicants also argued that the phrase "a soluble IL-21R" as used in the amended claims was not indefinite for a variety of reasons (*id.* at p. 24-27). However, these amended and now pending claims (for which the rejection has been withdrawn) still recite "an IL-21R" in the third wherein clause of claims 11 and 13, and in the first wherein clause of claims 24 and 25; thus, contrary to the Examiner's interpretation, the pending claims do not use the article "the" when referring to IL-21R.

It is unclear whether Applicants' previous arguments and amendments have been deemed persuasive by the Examiner (such that all indefiniteness-based rejections of claims 11, 13, 24 and 25 are withdrawn). Applicants respectfully request clarification.

II. Rejections Based on 35 U.S.C. §112, 1st Paragraph

A. Enablement-Based Rejection

Applicants' previous arguments related to the 35 U.S.C. §112, 1st paragraph, enablement-based rejection of claims 11, 13, and 20-25 were deemed partially persuasive by the Examiner (Office Action, dated October 4, 2006 at pp. 6-7). Specifically, the Examiner states that the arguments regarding: 1) the irrelevancy of agonistic soluble IL-21Rs to the claims, which recite antagonistic soluble IL-21Rs; and 2) the therapeutic usefulness of IL-21R antagonists, have been found persuasive (*id.*). Applicants would like to thank the Examiner for these comments.

The Examiner, however, maintains the 35 U.S.C. §112, 1st paragraph, enablement-based rejection of claims 11, 13, and 20-25.[1/] Specifically, the Examiner contends that while the

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[1/] Applicants note that in the previous Office Action, the Examiner also recited an enablement-based rejection of claims 17 and 18 (Office Action, dated March 7, 2006 at

specification enables a full-length antagonistic soluble IL-21R that is therapeutically effective, the specification does not enable any soluble antagonist IL-21R comprising an extracellular domain that is at least 85% identical to the extracellular portion of the IL-21R set forth in SEQ ID NO:4 and which possesses the therapeutic activities recited in the claims (Office Action, dated October 4, 2006 at p. 7). The Examiner asserts that practicing the instant claims would require substantial inventive contribution to determine which 15% of the human IL-21R sequence could be altered without changing the functional and structural requirements of the claims (*id.*). For the following reasons, this rejection is respectfully traversed.

The claims recite, *inter alia*, a soluble IL-21R comprising an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, wherein the extracellular domain of the soluble IL-21R is at least 90% identical to amino acids 20-235 of SEQ ID NO:4 (hereinafter "IL-21R variant"). To fall within the scope of the 90% identity requirement, the extracellular domain of the soluble IL-21R may contain up to 10% different amino acid residues from residues 20-235 of SEQ ID NO:4. Various well known methods exist that allow a skilled artisan to modify the amino acid residues of a polypeptide sequence (e.g., site directed mutagenesis of a polynucleotide encoding the polypeptide of interest [*see*, e.g., "Site Directed Mutagenesis" § 20-3 (pp. 738-744) in Basic Methods in Molecular Biology, 2nd Edition (1994) Davis et al. (Eds.) Appleton & Lange, CT] (submitted herewith as part of an Information

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p. 5). The Examiner does not recite this rejection in the present Office Action, and therefore Applicants believe the previous arguments and amendments have been found persuasive with respect to the enablement-based rejection of these two claims. Applicants respectfully request the Examiner to clarify whether claims 17 and 18 are no longer rejected as lacking enablement.

Disclosure Statement (IDS)). Thus, producing an IL-21R variant does not require undue experimentation.

As the production of an IL-21R variant is routine, the issue becomes whether undue experimentation would be required to determine if the IL-21R variant satisfies the additional claim limitations of: [1] solubility; [2] IL-21R antagonism; and [3] inhibition or reduction in the differentiation of a Thp cell or cell population into a Th2 cell or cell population, or increasing IFNγ levels in a T cell or cell population. That some experimentation (or even extensive experimentation) is required to determine whether an IL-21R variant meets these claim limitations does not in itself invalidate the claims under § 112 (*see In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (stating "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed")). If the experimentation required to determine if an IL-21R variant displays these properties is merely routine trial-and-error, or if the specification provides a reasonable amount of guidance to allow one of skill in the art to determine if an IL-21R variant displays these properties, then the enablement requirement is satisfied (*see In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal . . . ."); *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988)).

Applicants respectfully submit that any experimentation required to determine if an IL-21R variant displays the above-identified properties is routine, and that the specification additionally provides reasonable guidance to allow a skilled artisan to determine if an IL-21R variant displays the properties recited in the claims. *Heany* et al. ((1998) J. Leukocyte Biol. 64:135-146) (of record) indicates that the production of soluble receptors is routine in the art.

Thus, determining whether an IL-21R variant is soluble does not require undue experimentation. An IL-21R variant may be tested for antagonism of IL-21R by, e.g., a competition enzyme-linked immunosorbant assay (ELISA),[2/] which is a common technique used to identify receptor antagonists.[3/] Thus, determining whether an IL-21R variant is an IL-21R antagonist does not require undue experimentation. Finally, the specification provides techniques that allow one to determine if an IL-21R variant inhibits or reduces the differentiation of a Thp cell or cell population into a Th2 cell or cell population, or increases IFNγ levels in a T cell or cell population (see, e.g., Example 1-4, 6, and 9).[4/] Thus, determining whether an IL-21R variant displays the recited effects does not require undue experimentation, and any experimentation that might be required is well known and routine. As a result, no undue experimentation is required to determine if an IL-21R variant meets any of the recited properties.

Accordingly, no undue experimentation is required to make an IL-21R variant as set forth in the claims, and no undue experimentation is required to determine if that IL-21R variant is a soluble antagonist that inhibits or reduces the differentiation of a Thp cell or cell population into a Th2 cell or cell population, or increases IFNγ levels in a T cell or cell population. One desiring to produce IL-21R variants with the properties recited in claims 11, 13,

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2/ The soluble IL-21R fusion protein used in the experiments outlined in the U.S. Published Patent Application No. 2006/0039902 (submitted with the IDS filed on June 7, 2006) is an antagonistic soluble IL-21R molecule. Antagonism was determined by ELISA, which showed that the IL-21R fusion protein inhibited the binding of IL-21 to IL-21R (*see* U.S. Published Patent Application No. 2006/0039902 at paragraph [0240]).

3/ For example, the application teaches that IL-21 inhibits IL-12 activity in T cells (Specification at p. 43-45). This activity, which may be tested by, e.g., ELISA, may be used to determine whether an IL-21R variant is an antagonist of IL-21R.

4/ For example, Applicants state that one may use ELISA to measure IL-21-mediated changes in IFNγ levels at page 8, lines 16-18 of the instant specification.

and 20-25 need only follow Applicants' disclosure or any of the well-known and routine techniques available to one of skill in the art.

The Examiner contends that single amino acid changes can destroy protein function, and that the effects of amino acid changes are largely unpredictable (Office Action, dated October 4, 2006 at p. 7, *citing* Wells (1990) *Biochemistry* 29:8509-17). Thus, the Examiner concludes that substantial inventive contribution would be required on the part of a practitioner (*id.*). As discussed above, Applicants respectfully submit that neither the production of an IL-21R variant, nor the assaying of its properties requires any inventive contribution or undue experimentation. Applicants additionally note that *Wells*, which the Examiner relies on to support the Examiner's assertion of unpredictability, teaches

> removal of a single molecular contact by a point mutation causes relatively small reductions ... in the free energy of transition-state stabilization ..., or protein stability ... compared to the overall free energy associated with these functional properties ... . Thus, it is possible to modulate protein function by mutation at many contact sites. In fact, to design large changes in function will often require mutation of more than one functional residue.

(*Wells*, *supra*, at p. 8509). *Wells* suggests that: 1) a point mutation of a functional residue is not expected to affect a protein's function; and 2) mutating less than "many contact sites"[5/] of a protein is not expected to affect a protein's function. In contrast to the Examiner's contention, *Wells* does not indicate that Applicants have not provided information sufficient to allow one of skill in the art to make and use a genus of IL-21R variants without undue experimentation. *Wells*

5/ *Wells* is concerned with the effect of modifying amino acid residues on enzyme activity (*Wells* at p. 8509). *Wells* uses the phrase "contact site" to describe the substrate binding pocket of an enzyme and a protein binding pocket of a protein involved in protein-protein interactions (*id.* at p. 8509 and 8514). Importantly, *Wells* characterizes sites of protein-protein interaction as rigid interfaces where "mutations are unlikely to alter grossly the structure or mode of binding" (*id.* at. p. 8515).

suggests that changes in nonfunctional domains of IL-21R,[6/] and mutation at less than "many contact sites" of IL-21R, will not affect IL-21R activity. Accordingly, *Wells* provides guidance for one desiring to introduce amino acid changes in the IL-21R sequence while retaining the recited properties.

The MPEP states that when addressing claims that encompass inoperative subject matter, one must ask "whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)" (MPEP 2164.08(b)). As discussed above, after producing an IL-21R variant by known techniques, the properties of that variant may be assayed using only routine effort. *Wells* does not suggest that one of skill in the art would be

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[6/] Applicants have previously provided a variety of papers that a skilled artisan could use to identify domains of IL-21R that contribute to the elements recited in the claims (See Amendment and Response dated June 7, 2006 at pp. 10-13). Applicants also submitted several papers that exemplify the guidance available to one of skill in the art concerning what amino acid changes are likely to be phenotypically silent (i.e., changes that are unlikely to significantly affect IL-21R ligand-binding function) (Amendment and Response dated June 7, 2006 at p. 11). *Wells* also provides guidance concerning what amino acid changes are likely to be phenotypically silent, e.g., changes in domains of IL-21R that do not bind ligand, and changes in amino acids that do not interact with each other in the IL-21R ligand-binding pocket (*Wells* at p. 8509).

Further, Applicants resubmit herewith as part of an IDS two sequence alignments: "Amino Acid Sequence Comparison of Mouse and Human IL-21R;" and "Amino Acid Sequence Comparison of Human IL-21R and Human IL-2Rβ." These alignments, which were available to one of skill in the art at the time of filing the instant application, may be used by a skilled artisan in determining which residues of IL-21R may be altered without modifying IL-21R function.

Regardless of the valuable guidance available to allow a skilled artisan to determine what amino acid residues of IL-21R may be altered without modifying function, Applicants submit that such guidance is unnecessary and superfluous, as a skilled artisan may produce an IL-21R variant with the recited properties by mere trial and error and without undue experimentation.

unable to predict whether an IL-21R variant is inoperative or operative; rather *Wells* suggests amino acid modifications that a skilled artisan should avoid in order to produce an IL-21R variant that retains the recited properties. As the Examiner has not established that a skilled artisan would be unable to predict whether an IL-21R variant satisfies the claim elements, and Applicants have provided evidence that a skilled artisan would be able to determine whether an IL-21R variant satisfies the claim elements, Applicants respectfully submit that one of ordinary skill in the art could make and use the recited IL-21R genus without undue experimentation.

For at least these reasons, Applicants respectfully submit that the subject matter of claims 11, 13, and 20-25 is enabled, and request that the 35 U.S.C. § 112 enablement-based rejection of these claims be withdrawn.

B. Written Description-Based Rejection

The Examiner maintains the previous 35 U.S.C. §112, 1st paragraph, written description-based rejection of claims 11, 13, and 20-25. Specifically, the Examiner states that "while the specification contemplates a soluble IL-21R that is at least 85% identical to amino acids 20 to 235 of SEQ ID NO:4, that is capable of binding IL-21 receptor and displays all of the recited activities, it fails to disclose one single variant that possess[es] the recited activities" (Office Action, dated October 4, 2006 at p. 5). The Examiner states that the arguments presented in the previous response [i.e., (1) that the specification discusses IL-21R sequences with varying degrees of identity to the disclosed human IL-21R; (2) that alignment of a family of common gamma chain receptors derived from different species would indicate regions of IL-21R that should not be significantly altered or regions that should be altered only with similar amino acids to retain the desired functionality; (3) that the specification discloses the sequence of mouse IL-

21R, and hence discloses IL-21Rs with at least 38% divergence; (4) that several references teach receptors with identity to IL-21R, allowing one of skill in the art to follow these teachings to determine which residues of IL-21R could be modified to retain the desired functionality; and (5) that one of skill in the art could align the mouse and human IL-21Rs disclosed in the specification to identify residues amenable to substitution and therefore retain the desired functionality], are not persuasive because "[t]he issue is not the existence of receptors that share 85% homology to residues 20-235 of SEQ ID NO:4, but whether said receptors also retain the desired activity" (*id.* at pp. 3-6). For the following reasons, this rejection is respectfully traversed.

Applicants note the law does not require actual disclosure of IL-21R variants within the recited genus; rather the law merely requires Applicants to provide an adequate description of the recited genus. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 3223 F.3d 956 (Fed. Cir. 2002).[7/] For genus claims, the question is whether the specification discloses sufficient identifying information such that one of ordinary skill in the art could visualize or recognize the identity of the invention, i.e., whether the disclosed species, coupled with other descriptive information in the specification (e.g., structure, function, structure-function correlation, physical properties, chemical properties, etc.), provides information sufficient to represent the claimed genus. *Enzo*, 3223 F.3d 956 (Fed. Cir. 2002); *Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559 (Fed. Cir. 1997). Therefore, the previously presented arguments, which

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7/ The Examiner contends that Applicants must disclose variants within the recited genus, stating "[t]he issue is not whether the skilled artisan can figure out which amino acids [sic] residues to modify and which to conserve, *but whether the specification discloses variants that retain the recited functions*, to indicate that Applicants were in possession of the claimed genius [sic]." (Office Action, dated October 4, 2006 at page 6 (emphasis added)).

emphasize the other descriptive information in the specification that allows a skilled artisan to "visualize or recognize the identity" of IL-21R variants within the recited genus, are relevant to the issue of this written description rejection.

Applicants have previously argued that they have adequately described full length sequences of mouse and human IL-21R, boundaries of IL-21R extracellular domains (and hence soluble IL-21R), methods of making soluble IL-21R, and functions of soluble IL-21Rs (e.g., antagonistic). Applicants have also argued that one skilled in the art would have sufficient knowledge to recognize which amino acid within the sequence of the IL-21R are involved in ligand binding, and thus which residues should remain the same or be minimally altered in order to preserve receptor binding capabilities. Thus, one skilled in the art would be able to visualize and recognize the identity of IL-21R variants within the recited genus.

Moreover, Applicants submit that they have described, and thus possessed, a genus of soluble IL-21Rs, wherein a soluble IL-21R within the genus comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 90% identical to amino acids 20-235 of SEQ ID NO:4. Applicants have described both mouse and human IL-21R, with mouse IL-21R retaining 62% identity to human IL-21R. (See "Amino Acid Sequence Comparison of Mouse and Human IL-21R," submitted with the IDS filed June 7, 2006 and resubmitted herewith). Applicants have shown in the instant Application that, *inter alia*, mouse IL-21 inhibits production of IFNγ in developing mouse Th cells (Example 5 and Fig. 3B), mouse Th2 cells express IL-21 during a Th2 immune response (Example 2, Fig. 1D), and IL-21R-deficient mice mount an enhanced Th1 response (Example 9, Figs. 5A and 5B). One of skill in the art would fully expect human IL-21 and IL-21R to display properties similar to those Applicants have

shown for mouse IL-21 and IL-21R.[8/] Thus, the Examples in the instant application, which deal with the functional response of mouse cells to mouse IL-21 and IL-21R, indicate that Applicants possessed both mouse and human IL-21 agonists and antagonists. As mouse and human soluble IL-21Rs sequences differ by 38%, and the present claims recite a genus that differs from the human IL-21R sequence by at most 10%, Applicants have described the scope of the genus recited in the claims. Applicants note again that they have amended the claims to require the extracellular domain of the soluble IL-21R to be at least 90% identical to amino acids 20-235 of SEQ ID NO:4 (rather than 85% identical to amino acids 20-235 of SEQ ID NO:4).

For at least these reasons, Applicants respectfully request withdrawal of the written description-based rejection of claims 11, 13, and 20-25.

[8/] For example, mouse cells expressing mouse cytokine receptors respond similarly to human and mouse cytokine ligands. Fukushima and Yamashita ((March, 2001) *J. Biol. Chem.* 276:7351-56, 7353 (submitted herewith as part of an IDS)) state that the mouse cytotoxic T cell line CTLL-2 responds to human and mouse IL-2 similarly (*See also*, Gearing and Thorpe (1988) *J. Immunol. Meth.* 114:3-9 (showing that various laboratories study human IL-2 activity using mouse CTTL cells) (submitted herewith as part of an IDS)). Human IL-2 and mouse IL-2 have 55.6 % sequence identity (Yokota et al. (1985) *Proc. Natl. Acad. Sci. U.S.A.* 82 (1): 68-72, 72 (stating that 94 of the predicted 169 amino acids of mouse IL-2 are conserved in human IL-2) (submitted herewith as part of an IDS)). This suggests that cytokines that diverge by 44.4 % can still induce the same functional response.

III. Rejections Based on 35 U.S.C. §103

The Examiner has rejected claims 13, 17-23 and 25 under 35 U.S.C. §103(a), as unpatentable over Kasaian et al. ((April 2002) *Immunity* 16:559-69) ("Kasaian") in view of Brenne et al. ((May 2002) *Blood* 99:3756-62) ("Brenne"). Specifically, the Examiner states that Kasaian teaches that IL-21 enhances interferon gamma production in T cells and Brenne discloses a method of using anti-IL-21R antibodies or soluble IL-21R to neutralize IL-21 activities (Office Action, dated October 4, 2006 at p. 8). The Examiner concludes that it would have been obvious to devise the instant method claims directed to increasing interferon gamma in a T cell population with an antagonist of IL-21 based on the combination of Kasaian and Brenne (*id.* at p. 9). That rejection is respectfully traversed.

Kasaian teaches that IL-21 enhances IFNγ production in NK cells, not T cells. Kasaian states

> [p]reviously stimulated but not resting NK cells showed strong induction of cytolytic activity (Figures 4A-4C) and IFNγ production (Figure 5A) when exposed to IL-21. Experiments using FACS-sorted populations of >95% pure NK and T cells confirmed that both activities could be attributed almost exclusively to NK cells in these cultures... .

(Kasaian, page 563, column 1, first full paragraph, emphasis added). The instant claims are directed to a method of increasing IFNγ levels in a T cell or cell population, not NK cells.

Moreover, Kasaian teaches that IL-21 enhances IFNγ production in NK cells. (See Kasaian Abstract, pp. 561-62, and Figure 5A). The instant specification teaches that IL-21 decreases IFNγ production in T cells. (See *Specification*, Example 3). Thus, antagonists of IL-21 would be expected to decrease IFNγ production in NK cells, while the instant claims are directed to increasing the levels of IFNγ in T cells using antagonists of IL-21.

The deficiencies of Kasaian are not overcome upon combination of Kasaian with Brenne. Brenne also fails to teach or suggest a variety of elements of claims 13, 17-23, and 25 (e.g., contacting a T cell or cell population from a subject or sample of interest with an antagonist (or agonist) of IL-21 or IL-21R in an amount sufficient to increase (or decrease) IFNγ levels in said T cell or cell population). Thus, the combination of Brenne and Kasaian fails to teach or suggest all the elements of claims 13, 17-23 and 25.

For at least these reasons, Applicants respectfully request withdrawal of the outstanding obviousness-based rejection of claims 13, 17-23 and 25.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. § 112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

POWER OF ATTORNEY AND CORRESPONDENCE ADDRESS INDICATION FORM AND STATEMENT UNDER 37 CFR 3.73(b)

Applicants submit herewith a POWER OF ATTORNEY AND CORRESPONDENCE ADDRESS INDICATION FORM and a STATEMENT UNDER 37 CFR 3.73(b). Applicants respectfully request the Examiner to associate the new customer number (05514), and new attorney docket number (01997.043600) with the above identified application.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

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